

REMARKSInterview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

Status of the Claims*Pending claims*

Claims 1, 3 to 11 and 25 to 42 are pending and under consideration.

Claims added in the instant amendment

In the present response, claims 43 and 44 are added, and claims 26, 31 and 40 to 42 are canceled, without prejudice or disclaimer. Thus, after entry of the instant response, claims 1, 3 to 11 and 26 to 30, 32 to 39, 43 and 44, will be pending.

Outstanding Rejections

The rejection of claims 1, 3 to 11 and 25 to 36, under 35 U.S.C. §103, alleging these claims obvious over Morton, et al., WO 95/15338; hereinafter "Morton") in view of The Interferon Beta Multiple Sclerosis Study Group (Neurology, 1993, 43:655-661; hereinafter "the MS Study"), has been maintained. The rejection of claim 31 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite has been maintained. Claims 33 to 36 are newly rejected under 35 U.S.C. § 112, second paragraph. Claims 1, 3 to 11, 27 to 31 and 33 to 36, are newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement.

Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the claim amendments

The specification sets forth an extensive description of the invention in the new and amended claims. For example, support for methods of the invention wherein the IFN- β is administered at a dose that does not produce IFN- β -induced side effects in the individual, can be found, inter alia, on page 12, lines 10 to 13, of WO 00/43033 (the publication of the priority

document PCT/AU00/00032). Support for methods of the invention encompassing cpn10 and IFN- β combination therapy wherein cpn10 and IFN- β provide greater relief from disease symptoms than does IFN- β alone, thereby reducing the need for IFN- β to be administered at doses which produce side effects, can be found, inter alia, on page 13, lines 3 to 6, of WO 00/43033. Support for methods of the invention encompassing administering to an individual in need thereof a pharmaceutically-effective amount of the cpn10 and IFN- β , wherein the cpn10 is administered daily and the IFN- β is administered once weekly or thrice weekly, can be found, inter alia, on page 13, line 31, to page 4, line 5.

Accordingly, Applicants respectfully submit that no new matter is introduced by the instant amendment.

Issues under 35 U.S.C. §103

The rejection of claims 1, 3 to 11 and 25 to 36 under 35 U.S.C. §103 has been maintained, for reasons of record, for reasons set forth in paragraph 4, pages 2 to 6, of the OA. Applicants respectfully traverse and expressly incorporate their previous responses herein, including the submitted expert declaration by Dr. Johnson (see response of October 27, 2005).

As discussed in Applicants' last response, the discussion is clearer if the outstanding issues and rejections are organized by the three separate embodiments of the claimed invention:

(I) Synergistic action: In one embodiment, the invention provides methods of treating MS comprising administering to an individual in need thereof a pharmaceutically-effective amount of both cpn10 and IFN- β , wherein the therapeutic effect of administering both cpn10 and IFN- β is improved (synergistic) as compared to the therapeutic effect of administering the same amount of cpn10 or IFN- β alone.

(II) Suboptimal dosages: In a second embodiment, the invention provides methods of treating MS in an individual taken off IFN- β treatment or having reduced dose IFN- β treatment because of IFN- β -induced side effects, the method comprising the steps of administering to an individual in need thereof a combination treatment comprising pharmaceutically-effective amounts of both cpn10 and IFN- β , wherein the IFN- β is administered at a dose that does not produce

IFN- β -induced side effects in the individual. Synergistic action of cpn10 and IFN- β is not a limitation. See, e.g., independent claim 25.

(III) Delaying relapse of MS: In a third embodiment, the invention provides methods of delaying relapse to an active from an inactive state of MS, comprising (a) providing a pharmaceutical composition comprising both cpn10 and IFN- β , or providing two pharmaceutical compositions each comprising cpn10 or IFN- β , wherein one of the pharmaceutical compositions comprises cpn10 and the other pharmaceutical composition comprises IFN- β ; and (b) administering to an individual in need thereof a pharmaceutically-effective amount of the cpn10 and IFN- β .

Addressing these separate embodiments in turn:

(I) Synergistic action:

The rejection of claims directed to methods of treating MS comprising administering to an individual in need thereof a pharmaceutically-effective amount of both cpn10 and IFN- β , wherein the therapeutic effect of administering both cpn10 and IFN- β is improved (synergistic) as compared to the therapeutic effect of administering the same amount of cpn10 or IFN- β alone, was maintained based on, inter alia: (1) the allegation that neither the specification nor Dr. Johnson's submitted expert declaration show evidence of unexpected results, i.e., synergistic versus additive results upon administration of both cpn10 and IFN- β ; and (2) the Office's alternative interpretation of Jeffrey (2004) Neurology 63:S41-S46 (hereinafter "Jeffrey"). See, e.g., paragraph 4, starting on page 2, to line 5, of page 5, of the OA.

Applicants respectfully traverse, for reasons set forth in their last response of March 29, 2006 (see, e.g., pages 9 to 12, of that response). However, merely to expedite prosecution and allowance of this application, all pending claims directed to synergistic action have been canceled.

(II) Suboptimal dosages:

In a second embodiment, the invention provides methods of treating MS in an individual taken off IFN- β treatment or having reduced dose IFN- β treatment because of IFN- β -induced side effects, the method comprising the steps of administering to an individual in need thereof a combination treatment comprising pharmaceutically-effective amounts of both cpn10 and IFN- β ,

wherein the IFN- β is administered at a dose that does not produce IFN- β -induced side effects in the individual. All pending claims are now directed to this embodiment of the invention.

In their last response, Applicants averred that because neither Morton nor the MS study taught or suggested administering IFN- β in a combination therapy where the IFN- β is administered at dosages which would be clinically ineffective if IFN- β were given alone, e.g., doses that do not produce IFN- β -induced side effects in the individual, neither cited reference alone or in combination teaches or suggests the claimed invention.

In this OA, the Office maintained the rejection, alleging that it was routine in the art to optimize dosages administered to a patient to obtain an optimal clinical outcome (see, e.g., page 5, lines 5 to 10, of the OA).

However, Applicants' respectfully submit that administering a drug at dosages which, if not administered in combination with a second, different drug, would be ineffective is a significantly different fact pattern than "optimizing" an otherwise clinically effective dose. Administering a drug at a clinically ineffective dose is not merely "optimizing a workable range" by routine experimentation, which was the situation in the cited *In re Aller* (see, e.g., page 5, lines 11 to 13, of the OA). Also, as declared by Dr. Johnson in her supplementary declaration submitted in Applicants' last response, there was no understanding or teachings in the art at the time of the invention to lower an otherwise toxic (side effect-producing) and *clinically ineffective* dose of IFN- β and then combine a lower, *clinically ineffective* dose of IFN- β with cn-10 to realize an effective therapy for MS. This was discovered for the first time by the inventors of this claimed invention.

(III) Delaying relapse of MS

In a third embodiment, the invention provides methods of delaying relapse to an active from an inactive state of MS, comprising (a) providing a pharmaceutical composition comprising both cpn10 and IFN- β , or providing two pharmaceutical compositions each comprising cpn10 or IFN- β , wherein one of the pharmaceutical compositions comprises cpn10 and the other pharmaceutical composition comprises IFN- β ; and (b) administering to an individual in need thereof a pharmaceutically-effective amount of the cpn10 and IFN- β . See, e.g., independent claim 26.

Applicants respectfully maintain that neither Morton nor the MS study teach or suggest using the combination of cpn10 and IFN- β to delay relapse to an active from an inactive state of MS. Additionally, the therapeutic effect of administering both cpn10 and IFN- β is improved (synergistic) as compared to the therapeutic effect of administering the same amount of cpn10 or IFN- β alone.

Applicants respectfully traverse, for reasons set forth in their last response of March 29, 2006 (see, e.g., page 12 of that response). However, merely to expedite prosecution and allowance of this application, all pending claims directed to only to an active from an inactive state of MS have been canceled; and after entry of the instant amendment, all claims are directed to methods encompassing administering IFN- β in a combination therapy where the IFN- β is administered at dosages which would be clinically ineffective if IFN- β were given alone, i.e., doses that do not produce IFN- β -induced side effects in the individual.

There was a long-felt need to administer both cpn10 and IFN- β

The Office further alleges that Applicants' showing of long-felt need was insufficient because there is no evidence that if persons skilled in the art knew of the teaching of the cited references, they would still be unable to solve the problem (see, e.g., page 6, lines 6 to 14, of the OA), and cites MPEP §716.04, which sets forth the three factors that must be met for a satisfactory showing of "long-felt need":

Establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. ... Second, the long-felt need must not have been satisfied by another before the invention by applicant. ... Third, the invention must in fact satisfy the long-felt need. MPEP §716.04, pg 700-276, 8th 3d. Rev. 3, Aug. 2005. (emphasis added)

Applicants respectfully aver that all three factors showing long-felt need have been met. Regarding the first factor, as declared by Dr. Johnson (see, e.g., paragraphs 4 and 5, of the declaration submitted in Applicants' last response) at the time of the invention multiple sclerosis (MS) was recognized as a debilitating disease and physicians had long sought an effective therapy, but with limited success. Regarding the second factor, as acknowledged by the Office (see e.g., page 3, lines 13 and 14, of the OA), no one had practiced, suggested or provided any motivation to

specifically combine both cpn10 and IFN- β into a combination therapy. Regarding the third factor, and as declared by Dr. Johnson in her supplementary declaration submitted in Applicants' last response, there was no understanding or teachings in the art at the time of the invention to lower an otherwise toxic (side effect-producing) and *clinically ineffective* dose of IFN- β and then combine a lower, *clinically ineffective* dose of IFN- β with cn-10 to realize an effective therapy for MS. This was discovered for the first time by the inventors of this claimed invention.

Accordingly, in view of Applicants remarks herein and their previous response submissions, including Dr. Johnson's previous declarations, and the instant amendment, the rejection under 35 U.S.C. §103(a) can be properly withdrawn. Additionally, in view of the evidence of secondary indicia of nonobviousness, as supported by the declarations of Dr. Johnson, Applicants submit that they have rebutted any possible *prima facie* case of nonobviousness. Accordingly, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. §103(a).

Issues under 35 U.S.C. §112, second paragraph

The phrase "clinically significant"

The rejection of claim 31 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite has been maintained, see, e.g., section 5, pages 6 to 7, of the OA. In particular, it is alleged that the phrase "clinically significant IFN- β -induced side effects in the individual" is vague in that it is not defined in the specification.

As noted in their previous response, it was well known in the art at the time of the invention that IFN- β administration at certain dosages could produce side-effects, and it was well known what those side effects were; see, e.g., page 13, lines 15 to 23, of the specification. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail in the specification.

While the Office alleged that it was unclear what a clinically significant IFN- β -induced side effect in an individual was (see the sentence spanning pages 6 to 7, of the OA), the Office also stated that "it is [was] routine in the art to optimize the dosage administered to a patient to obtain optimal clinical outcome" (see, e.g., page 5, lines 5 to 10, of the OA). Applicants respectfully submit that the time of the invention "clinically significant IFN- β -induced side effect" was an art-

accepted and well understood term, and one skilled in the art of treating MS patients would have understood with no ambiguity exactly what was a clinically significant IFN- β -induced side effect.

However, as the Office remains concerned with the phrase “clinically significant”, the instant amendment also addresses this issue.

The phrase “equivalent of administering”

Claims 33 to 36 are newly rejected under 35 U.S.C. § 112, second paragraph. In particular, the Office was concerned about the phrase “equivalent of administering.” The instant amendment addresses this issue.

Rejections under 35 U.S.C. §112, first paragraph - enablement description

Claims 1, 3 to 11, 27 to 31 and 33 to 36, are newly rejected under 35 U.S.C. § 112, first paragraph, enablement requirement, see, e.g., section 7, pages 7 to 9, of the OA.

The Office noted that the specification is enabling for the treatment of MS by administration of cpn10 and IFN- β (see e.g., first sentence of section 7, page 7, of the OA).

However, it is alleged that the specification does not provide reasonable enablement for the claimed improved “synergistic” treatment of MS by administering cpn10 and IFN- β , and the Office repeats its detailed reasoning of why the specification allegedly does not provide sufficient evidence of a synergistic MS treatment effect when co-administering cpn10 and IFN- β . Applicants have provided argument and evidence, including Dr. Johnson’s expert declaration, that there is a synergistic MS treatment effect when co-administering cpn10 and IFN- β , including co-administering cpn10 with doses of IFN- β that otherwise would be ineffective if the IFN- β were administered alone.

However, merely to expedite prosecution and allowance of this application, after entry of the instant amendment, all claims will be directed to methods encompassing administering IFN- β in a combination therapy where the IFN- β is administered at dosages which would be clinically ineffective if IFN- β were given alone, i.e., doses that do not produce IFN- β -induced side effects in the individual.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs, and 35 U.S.C. §103(a). In view of the above, claims in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 284502000600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at (858) 720-5133.

Dated: October 16, 2006

Respectfully submitted,

By

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